REMARKS

Applicant respectfully requests reconsideration of this application in view of the amendments and remarks made herein.

Claims 1-11, 13-14, 17-18, 21 and 24-27 are pending. Claims 22, 23 and 28-49 are canceled. Claims 12, 15-16, and 19-20 are withdrawn from consideration with the understanding that said claims will be reintroduced upon allowance of a generic claim.

1. Substance of the Interview

Applicant thanks the Examiner, Amber D. Steele, for the courtesies extended to Applicant's representatives during the interview of March 15, 2007. During the interview, the §102 and §103 rejections were discussed.

2. Summary of the Invention

The present invention relates to a method for proteomic analysis of a heterogeneous sample of peptides, or protein or peptide fragments. The key features of the method of the present invention are that the heterogeneous sample is separated into discrete *heterogeneous* classes, and that the *mass* and *abundance* of peptides, or protein or peptide fragments *in those heterogeneous classes* are determined. As explained below, there is nothing in the prior art that teaches, or even suggests, that one of skill in the art should analyze a heterogeneous sample of peptides, or protein or peptide fragments by separating that sample into discrete *heterogeneous* classes, and then determining the *mass* and *abundance* of peptides, or protein or peptide fragments, in those heterogeneous classes. Moreover, as explained further below, this combination of method features provides important advantages to the user, such that one can generate a profile of complex protein samples using relatively simple arrays with a lower number of binders.

As disclosed in the specification, one of the disadvantages of prior art methods for proteomic analysis was the very large numbers of protein-specific binders required to achieve this analysis (see, page 3 lines 15-22). In general, the prior art methods for protein sample analysis used "binders" (i.e. molecules with a specific binding affinity) designed to be specific for individual proteins (or fragments derived therefrom) in a sample and so, for example, in order to analyze a sample of 2000 different proteins one needed to individually isolate each of those 2000 proteins in advance, generate a specific binder (e.g. an antibody) to each protein, and then produce an array with each of those specific binders immobilized thereon. Such prior art methods were time-consuming and labor-intensive and presupposed an advanced knowledge of the identity of individual proteins within a sample in order to generate a specific binder for each protein.

The present invention has overcome these disadvantages. For example, no advanced knowledge of the identity of individual proteins in a protein sample is required in order to perform the method of the present invention because a standard array of binders can be used for any sample. Moreover, much lower numbers of different binders are required than the methods employed by the prior art. This is because the present invention employs binders that can each bind to peptides and protein and peptide fragments from divergent sources. Since the binders used in the present invention are not specific for an individual protein source, they can each bind multiple unrelated protein and peptide fragments. Accordingly, a less than 1:1 ratio between binders and proteins in a sample can be utilized. This makes the production and use of arrays much more economical and labor-efficient than those required to implement the prior art methods.

The present invention overcomes the disadvantages of the prior art methods by a unique interrelationship between the binding and characterizations steps. The binding steps of the present invention involve separating peptides, or protein or peptide fragments, into distinct classes irrespective of the parent proteins from which they were derived. The only

distinguishing feature of each class is that the molecules bound in any given class will all contain the same motif, e.g. the same C-terminal tri- or tetra-peptide sequence. Thus, the variety of peptides, or protein of peptide fragments bound to a given type of binder can differ in sequence at all positions other than the common motif, i.e. a heterogeneous class of peptides, or protein or peptide fragments, will be bound to any given type of binding molecule. As a result of this, lower numbers of binders are required in order to capture a useful proportion of peptides, or protein or peptide fragments, in a sample and, moreover, no advanced knowledge of the identity of proteins in a sample is required – on the contrary, a standard array can be used to analyze any sample of proteins.

However, because the peptides, or protein or peptide fragments, bound by each type of binding molecule in the method of the present invention are heterogeneous, their separation during the binding step is incomplete. Such incomplete separation could not be tolerated by those prior art methods that provide for the determination of protein abundance in a sample (e.g., including the prior art reference Barry cited by the Examiner) because they rely on having *homogeneous* classes at each location on an array so as to allow the user to correlate protein abundance at a given array location with the abundance of a specific bound protein.

Alternatively, those prior art methods for protein sample analysis that suggested that heterogeneity (i.e. incomplete separation) could be tolerated following the separation of a sample on an array (e.g., including the prior art reference Minden cited by the Examiner) did not attempt to determine the abundance of the different species bound within the thus-formed heterogeneous classes. Rather, in the case that heterogeneity was tolerated by such prior art methods, it was taught that it was necessary to provide multiple binders at different locations on an array to bind multiple different fragments *from the sample single protein*, in order to create binding patterns on the array that are characteristic of each protein, thereby to identify individual proteins. Such methods did not provide for the determination of abundance.

However, in the case of the present invention, the incomplete separation during the binding step of peptides, and protein and peptide fragments, derived from different parent proteins (i.e. the creation of heterogeneous classes) can be tolerated in a method that involves the determination of, *inter alia*, the *abundance* of the peptides, or protein or peptide fragments, *in the heterogeneous classes*. This is because the molecules in each class are characterized to determine the different masses of molecules in each class and the relative abundance of molecules of each mass in a given class. Thus, molecules derived from different parent proteins are distinguished on the basis of mass *and* abundance.

By combining the information derived from the binding and characterization steps it is possible to derive a picture of the protein sample analyzed, through a simple and time-efficient method that requires no advanced knowledge of the individual proteins in the sample being analyzed and employs only a single binding affinity step.

3. The Rejections Under 35 U.S.C.§ 102(e) Should Be Withdrawn

Claims 1-11, 13-14, 17-18, 21, 25, and 27 are rejected under 35 U.S.C. §102(e) as being anticipated by Minden et al. WO 02/086081 ("Minden").

According to the Examiner, Minden teaches methods of identifying a protein via assigning (e.g. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set. In addition, Minden is said by the Examiner, to teach that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized. The Examiner refers to paragraphs [003-004], [0030], [0036], [0048] and Figures 7-9.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference

shows exactly what is claimed. . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984).

Applicant maintains that step (b) of Claim 1 recites a step that includes a determination of the *mass* and *abundance* of peptides, or protein or peptide fragments, in the heterogeneous classes. Applicant asserts that Minden *does not specifically teach determining the abundance of the proteins*.

During the interview conducted with the Examiner on March 15, 2007, the Examiner expressed her belief that determining the "mass" and determining the "abundance" of a polypeptide using general mass spectrometry could possibly be viewed as the same characterization. Applicant respectfully disagrees with the Examiner on this point. Mass spectrometry is a central analytical technique most generally used to determine the composition of a physical sample by generating a mass spectrum representing the *masses* of sample components. Such a characterization does not necessarily involve a determination of the *abundance* of a polypeptide. As indicated above, Applicant's claims are limited by the inclusion of a step that *requires both* a determination of the *mass* and *abundance* of polypeptides. It follows that it is abundantly clear from the language of claims alone, that the determination of mass and the determination of abundance refer to two quite distinct types of characterization. Given that Minden fails to disclose the determination of the abundance of polypeptides, Minden cannot anticipate the presently claimed invention. Applicant respectfully requests that the rejection under 35 U.S.C.§ 102(e) be withdrawn.

4. The Rejections Under 35 U.S.C. §103 Should be Withdrawn

Claims 1-11,13-14,17-18, 21 and 24-27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Minden and Barry et al. WO 0225287 ("Barry").

According to the Examiner, Minden teaches methods of identifying a protein via assigning (e.g. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set. Minden is alleged to further teach (i) that the total protein content of a cell or tissue can be utilized as the protein mixture; (ii) that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin; (iii) that trypsin cleavage forms a peptide or epitope (e.g. motif) with C-terminal lysine or arginine residues; (iv) that the peptides or epitopes (e.g. motifs) can be at least three amino acids in length and can have at least two variable amino; (v) that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents; that the protein mixture may comprise all (e.g. 100%) of the proteins and that the epitopes cover the binding mixture; (vi) that the array can have 2-100 different proteins; (vii) that the binding reagents can be antibodies; (viii) that the proteins can be compared to a reference set; (ix) that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized; (x) that the reference set can include prediction about binding based on the predicted digests of a protein mixture (e.g. unfragmented); and (xi) that various binding reagents can be compared to a reference set or to other binding reagents.

The Examiner alleges that, although Minden does not specifically teach determining the abundance of the proteins or the use of desorption mass spectrometry or collision induced dissociation mass spectrometry, Barry teaches methods of (i) determining the binding and mass of trypsin digested proteins (including antibodies) from a cell (including phage) or tissue sample immobilized on an array (please refer to the abstract, pages 2-6, 21-30, Figures 3-6 and 8-10, Examples 2-3); (ii) determining the abundance of proteins via MALDI-TOF;

MALDI-TOF (matrix assisted laser desorption ionization-time of flight) mass spectrometry (e.g. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry or CID); and (iii) determining the abundance of the protein.

Applicant submits that the Office has not set forth a *prima facia* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

The present invention relates to a method for proteomic analysis of a heterogeneous sample of proteins, or protein or peptide fragments by *separating the sample into heterogeneous classes* at spaced apart locations on an array wherein no advanced knowledge of the identity of individual proteins in a protein sample is required in order to perform the method of the present invention.

As indicated above, the method of the invention recites a step that includes a determination of the *mass* and *abundance* of peptides, or protein or peptide fragments, in the heterogeneous classes that are bound to the array. Information on the abundance of proteins (i.e. quantitative information) in a sample can be just as, if not more, important than information on the presence or absence of a particular protein (i.e. qualitative information). For example, a disease-related protein may be expressed in both a disease and non-disease state, but at different levels. Applicant asserts that there is nothing in Minden to suggest that *quantification of proteins* in the array-bound heterogeneous classes is desirable, much less possible.

According to the Examiner, although Minden may not specifically teach determining the abundance of the proteins, Barry provides an abundance determination step to apply to Minden's method. In this regard, it is critical to note that Barry only teaches a method of

proteomic analysis *wherein each binding reagent corresponds to one protein* and requires advanced knowledge of proteins in the sample in order to generate an appropriate array of binders. In other words, Barry only teaches the determination of abundance wherein the analysis is applied to *homogeneous* classes of array-bound proteins. This is contrast to the present invention which relates to a method of determining the mass and abundance of a *heterogeneous class of array-bound peptides, or protein or peptide fragments*. Thus, if anything, one skilled in the art reading Minden in combination with Barry would only be motivated to form *homogeneous* classes of proteins as set forth by Barry, before determining the abundance of proteins in each homogeneous class. Thus, in fact, Minden in combination with Barry *teaches away* from the present invention which clearly requires a determination of the abundance of peptides/fragments of different mass within a *heterogeneous class*. Applicants maintain that, indeed, it is the basis of the present invention to provide a means for complex sample evaluation with relatively small arrays.

Applicants assert that a *prima facia* case of obviousness has not been established. In light of these remarks, Applicant respectfully requests that the obviousness rejections be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is believed that the subject claims are in condition for allowance, which action is earnestly solicited. If, in the opinion of

the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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